Detection of NO with a semi-conducting compound and a sensor and device to detect NO

The invention relates to the detection of nitric oxide, NO, in a gas mixture, such as produced during the respiratory cycle of a living organism, so that it becomes possible to determine whether the current lung function belonging to a living organism is normal, or deviates from a predetermined normal level.

It is known that alveolar cells and the respiratory tract epithelium produce endogenous nitric oxide and that this nitric oxide is secreted into the air in the respiratory ducts and/or lungs. This portion of secreted nitric oxide can thus be measured in exhaled air.

Further it is known that an evaluation of the production of endogenous nitric oxide in the lungs and respiratory ducts provides a measurement of the condition and/or function of the lungs and respiratory ducts, i.e. the lungs' condition or function.

It is further observed that in the case of inflammatory lung diseases, such as asthma and alveolitis, the nitric oxide concentration of the exhaled air is higher than normal, since the nitric oxide concentration has increased because of the inflammation. The nitric oxide concentration can thus be used as an indicator of an inflammation in the lungs and of inflammatory diseases, such as asthma or any allergic condition resulting in an inflammation of the lungs and/or respiratory tract.

Asthma constitutes a serious and growing global health problem. Nowadays, about 25 million people in Europe suffer from asthma.

Respiratory gas analysis is a simple, non-invasive method, which can be used for clinical routing measurement of inflammation.

At present exhaled breath analysis is performed only in the function laboratories of medical centers, using chemiluminescent analyzers. These NO analyzers utilize a photochemical reaction between NO and ozone:

$NO + O_3 \rightarrow NO_2$ (and NO_2*) + O_2.

NO_2*→ NO_2 + hν.

Approximately 10-20% of the NO_2 formed is produced in an electronically excited state (NO_2*), undergoing a transition to the ground state thereby emitting light. Light is emitted in the wavelength range of 590-2600 nm, and its intensity is proportional to the mass flow rate of NO through the reaction chamber. The detection limit for NO is approximately 1 ppb, which is sufficient considering the levels of exhaled NO in subjects with a normal or abnormal physiology (0-200 ppb). The disadvantages of chemiluminescent analyzers for NO detection are that they are relatively expensive (typically $ 40.000) and that the equipment is bulky (e.g. not portable). These aspects make chemiluminescent analyzers less attractive for use at the home (in the case of personal health monitoring) or by family practitioners. Therefore, it would be very advantageous to have a NO sensing device which is relatively low-cost and miniaturized so that it can be used for instance in the form of a disposable device for personal health monitoring.

Such a process and device, as well as a sensor to be used in said device, have now been found: they are more specifically based on the use of an organic semi-conducting compound.

The invention thus relates, in a first aspect, to the use of an organic semi-conducting compound for detecting NO.

Generally, detectors for sensing gases using *organic* semi-conducting compounds are known, and these are often referred to as electronic noses. However, no specific examples to detect NO have been described in the literature. Furthermore, also *inorganic* semi-conducting compounds are used as gas detectors, and a specific example to detect NO is known from B. Fruhberger et al., Sensors and Actuators B76 (2001), 226-234. This sensor is based on a WO_3 thin film chemiresistive sensor element, operating at elevated temperatures (250°C). This sensor element, however, is not specifically sensitive to NO, therefore additional filters are needed to measure NO in a complex gas mixture such as the human breath.

The present invention deals with an organic semi-conducting compound which is in itself able to react with nitric oxide. Therefore, in principle no extra filters are needed and the sensor can operate at ambient temperatures.

Preferred embodiments of the present use are claimed in claims 2-4.

It is observed that the use of thiophenes as a conducting polymer for the detection of a gas in so-called electronic nose conductivity sensors is mentioned per se in WO02/44698. The use of any thiophene for detecting nitric oxide, NO, is nevertheless not mentioned or suggested in this reference.

In the present use, pentacene is the preferred semi-conducting compound because it has the advantage that it is non-reactive towards water and oxygen, which are both main constituents of (exhaled) air.

The present invention relates in a second aspect to a process for measuring the amount of NO in a gas mixture containing NO, wherein said amount of NO is measured by using an organic semi-conducting compound, the electrical property of which changes upon reaction with NO, said change being utilized as a direct or indirect measure for the amount of NO being present in said gas mixture.

Preferred embodiments of the present process are claimed in claims 6-10.

A sensor for monitoring NO in a gas mixture, a FET type element and a device for determining the NO content of an air mixture are claimed in claims 11-17, 18-20 and 21-22 respectively, and will be explained hereinafter with reference to the accompanying drawing, wherein

Fig. 1 is a schematic representation of a planar FET type element,

Fig. 2 is a representation of the change in conductance (σ) of a semi-conducting compound according to the invention, upon reaction with NO,

Fig. 3a is a representation of a carbon nanotube based sensor,

Fig. 3b is an enlarged view of an array of carbon nanotubes aligned between two metal electrodes in a carbon nanotube based sensor according to Fig. 3a,

Fig. 4 is a schematic representation of a device for determining the NO production during breathing, according to the invention.

As has been indicated above, organic field effect transistors are claimed for the detection of nitric oxide. Organic semiconducting materials can therefore be applied in a well-known conventional planar FET structure or in a nanoscale FET configuration, as will be discussed hereafter.

Conventional planar FETs.

A planar field effect transistor (FET) is given in Fig. 1, and consists of several layers: a gate electrode 3, a dielectric layer 5 and source/drain contacts 1 and 2. In this case the dielectric is covered with an organic semiconducting material 4. Binding of the NO to the organic semiconducting material then results in depletion or generation of charge carriers within the transistor structure. An attractive feature of such a so-called chemically activated FET is that the binding of nitric oxide can be measured by a direct change in conductance or a related property.

Such a change in conductance is schematically represented in Fig. 2, where the y-axis represents the conductance σ and the x-axis represents the time t. Time point t0 represents the time when the organic semiconducting compound comes into contact with NO.

Obviously, the thickness and the dopant concentration of the organic semiconducting layer are important parameters to achieve optimal sensitivity: thinner layers and low-doped or intrinsic materials, for example, will respond to lower NO concentrations, but will be more quickly "saturated".

Nanoscale FETs.

To further improve the sensing properties of the conventional planar structure, nanoscale FETs can be used. Examples of such nanoscale devices are given in recent papers by Cui, Wei, and Lieber in Science **293**, 1289 (2001) and Kong, Franklin, Zhou, Chapline, Peng, Cho, and Dai in Science **287**, 622 (2000). A schematic representation of such a nanowire or nanotube sensor is given in Fig. 3a and 3b, and comprises metal electrodes 6 and 7, which are bridged by multiple nanowires or nanotubes 8a-8d. Binding of nitric oxide to the surface of a nanowire or nanotube can result in depletion or generation of charge carriers in the "bulk" of the nanometer diameter structure. In principle, single molecule detection is possible. The sensitivity and selectivity of the nanoscale FETs towards nitric oxide is obtained by covering the nanowires or nanotubes with the layer of organic semiconducting material according to the invention.

Nanowires may be grown by for example the so-called vapor-liquid-solid (VLS) growth method using a surface with for instance gold particles that act as catalytic growth centers, see Xiangfeng Duan and Charles, M. Lieber in Advanced Materials **12**, 298 (2000). A broad range of binary and ternary III-V, II-VI, IV-IV group elements can be synthesized in this way such as GaAs, GaP, GaN, InP, GaAs/P, InAs/P, ZnS, ZnSe, CdS, CdSe, ZnO, SiGe etc. The diameter of the nanowires may be controlled on a rough scale by

the size of the catalytic Au particles. If needed, fine-tuning of the diameter of the nanowires may be achieved through photochemical etching, whereby the diameter of the nanowire is determined by the wavelength of the incident light during etching.

Further, the sensitivity of the nanowire-based sensor can, if necessary, be improved by applying an organic semi-conducting layer on top of the nanowires.

Fig. 4 shows, schematically, a device 9 for determining the NO production during breathing. This device 9 comprises a conduit 12 having a mouthpiece 13 at one end thereof for inhalation or exhalation of air through the device. Conduit 12 is connected at the other end with an adjustable valve 14 which can be actuated (selectively) to deliver an air sample to conduit 12 from conduit 11 or to pass a sample of breathing air from conduit 12 to conduit 10. Valve 14 will be actuated to connect conduit 11 with conduit 12 (and thus to close conduit 10) in the event of a sub-pressure in conduit 12, induced by inhalation of an air mixture by a human being at mouthpiece 13. Valve 14 will be actuated to connect conduit 10 with conduit 12 in the event of an overpressure induced in conduit 12 due to exhalation by a human being at mouthpiece 13.

Conduits 10 and 11 are connected with measuring chambers 15 and 16 respectively, which are provided with sensors as explained in Fig. 1 and Figs. 3a, b, for measuring the NO content as a change in conductance of the CHEM-FET structure of the sensors.

In addition, a change in the gate potential in response to the NO absorption/reaction can also be used to monitor the NO content in the air sample flowing through the measuring chamber.

Although not shown, device 9 also comprises a flow meter, necessary for airflow measurement. Further, a cooling unit may be provided upstream of the measuring chamber to remove water from the air sample to be measured. A cooling unit is not necessary however when pentacene is used as the semi-conducting compound because it is non-reactive towards water.

The sensor in measuring chamber 16 will measure the NO background in air (when air is inhaled). The sensor in measuring chamber 15 will measure the NO content of exhaled air. Measuring chambers 15 and 16 are coupled with a signal processor 17, adapted to calculate the endogenous NO production on the basis of the difference (or any other algorithms) between the reading of the sensor present in measuring chamber 15 and the reading of the sensor present in measuring chamber 16. Preliminary evidence exists that the

amount of endogenous NO is not affected by the amount of atmospheric NO. In that case the measuring chamber may be omitted.

In a further modification of the present device, only the NO content of the exhaled air will be measured. Device 9 will then not comprise measuring chamber 16 and conduit 11 (this embodiment has not been shown).

From the above, it will be obvious that the electrical detection of NO using the CHEM-FET structure allows miniaturization and integration with Integrated Circuit technology.

The invention has been described by reference to certain preferred embodiments; however it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.